Non-Clinical Safety Assessment of Vaccines

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Objectives

- Regulatory requirements
- Key components in non-clinical evaluation
- Potential safety concerns
- Challenges/goals pertaining to toxicity assessments for vaccines
- CBER approach to toxicity assessment of vaccines
- CT products: Special considerations

Definition of Vaccine

- **“a heterogeneous class of medicinal products containing antigenic substances capable of inducing specific, active and protective host immunity against an infectious agent or pathogen**
  - **Preventive vaccines**
    - **Pre- and post-exposure prophylaxis**
  - **Therapeutic vaccines against infectious disease**

Regulatory Jurisdiction: Vaccines

- OVRR/CBER regulates preventive and therapeutic vaccines for infectious disease indications
  - Toxicology review
    - OVRR/CBER
    - CDER consult review

Vaccine Regulatory Requirements

- 21 CFR 610 – General Biological Product Issues
- Lot release
  - Potency
  - General Safety/Abnormal Toxicity
  - Sterility/Bioburden
  - Purity – moisture, pyrogenicity
  - Identity
  - Constituent Materials
    - All ingredients shall meet accepted standards of purity and quality: Certificate of analysis provided to IND
    - Adjuvant may be included if no AE on safety and potency (21 CFR 610.15)

Vaccine Regulatory Requirements

- **21 CFR 312 – IND regulations**
  - **312.23 (a)(7) – Chemistry/ Composition, manufacturing and Control Information**
    - **Assure proper identification, quality, purity and strength of product**
    - **Stability for the planned duration of trial**
  - **312.23(a)(8) – Pharmacologic and Toxicologic studies**
    - ***In vivo* or in *vitro studies* to conclude that proposed clinical studies are reasonably safe (GLP)**

Key Components in Non-clinical Assessment

- **Product characterization**
- **Manufacturing process**
  - **Starting materials**
  - **In-process controls for intermediates**
  - **Validated process procedures**
  - **Consistency in manufacture**
  - **Lot release**
    - **Adequate specifications**
    - **Purity, potency, identity**
  - **Stability**
- ***In vitro* studies**
- **Animal studies**
  - **Immunogenicity**
  - **Pyrogenicity testing**
  - **General safety testing**
  - **Neurovirulence testing**
  - **Reversion to virulence**
  - **Biodistribution studies**
  - **Integration studies**
- Safety studies
- Efficacy studies
  - **CT products**

Definition: Preclinical & Nonclinical Safety Assessment

- **Pre-clinical safety assessment**
  - **Includes product characterization, proof of concept studies, animal safety testing**
  - **Prerequisite to the initiation of clinical trials**

- **Non-clinical safety assessment**
  - **Preclinical safety assessment plus further product characterization and safety assessments during various stages of clinical product development**
    - **Includes studies if changes to the product manufacturing and/or formulation are made**
    - **Evaluates potential safety concerns that may have arisen from Phase 1 and Phase 2 clinical trials**

Vaccine Safety:

- Major Public Concern in Developed Countries
- Majority of vaccines given to healthy individuals
  - Public expects safe (and effective) products, especially vaccines given to healthy individuals (children)
- Perception of risk outweighs perception of benefit
  - For CT products, in emerging event, balance may shift
- Focus on non-clinical safety assessment including toxicity testing

Pre-clinical Safety Evaluation: Goals

- **To support entry into clinical trials, where human safety is ultimately evaluated**
  - **Rare toxicities, or potential effects of sub-populations often only addressable in humans**
- **Maximize the benefit-to-risk of vaccine development**
- **Determine a safe dose**
- **Identify any potential or unknown toxicities, target organs**

Broad measures	**Þ**	**unpredictable toxicity**
Specific assays	**Þ**	**key theoretical concerns**

CBER Precedence for Toxicity Studies for Vaccines

- Immunization of pregnant women
- Route of administration
- Novel adjuvants/novel antigens
- Adverse effects observed in clinical trials
  - Potential toxicity of vaccine assessed in non-clinical trials designed to replicate specific clinical events

Potential Safety Concerns

- Inherent toxicity of the vaccine
- Toxicity of impurities/contaminants
- Toxicity due to interaction of components
- Toxicity linked to the immune response induced

Toxicity Assessments of Vaccines: Challenges

- **Vaccines – complex, diverse class of biological products**
- **Act through complex mechanism whereby the product itself is not the final triggering component; elements of the immune system are the effectors**
- **Challenges:**
  - **Applicability of drug toxicity testing programs?**
  - **Applicability of available documents?**
  - **Timing of toxicity studies?**
  - **What products?**

Currently Available Guidance for Toxicity Assessments

- **CPMP Note for guidance on pre-clinical pharmacological and toxicological testing of vaccines, 6/1998**
- **ICH S6 Pre-clinical safety evaluation of biotechnology-derived Pharmaceutical, 7/1997**
- **ICH S5a Detection of Toxicity to Reproduction for Medicinal Products, 1994**
- **US FDA Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive & Therapeutic Vaccines for Infectious Disease Indications, 2000 (*revised*)**

Workshop on Non-clinical Safety Evaluation of Vaccines (December 2&3, 2002)

- Discussions on non-clinical methods for safety assessments of vaccines
  - Animal models
  - Study design (dose, ROA, schedule)
  - Endpoints (parameters evaluated)
  - Alternative methods
- Provided basis for the development of guidance
- http://www.toxicology.org.memberservices/meetings/cct-vaccines.html

General Principles of Non-clinical Evaluation of Vaccines

- **Risk/benefit**
  - **Target population**
  - **Clinical indication**
  - **Available clinical data**
  - **ROA**
  - **Mechanism of action**
  - **Product features, e.g., novelty**
  - **Relevant animal models**
- **USE SCIENTIFIC JUDGMENT!**

General Principles of Non-clinical Evaluation of Vaccines (cont.)

- Adequate to identify/characterize toxic effects
- Need and design based on scientific judgment and best available science
- No one study design for all product categories!
- May not be needed for all products

General Principles of Non-clinical Evaluation of Vaccines (cont.)

- **Need for balance in interpretation of nonclinical data**
- **Parameters to be considered:**
  - **Animal species/strain, dosing schedule, dose, ROA, devices, product features**
- **Evaluation of potential toxic effects:**
  - **Target organs, dose, routes of exposure, frequency of exposure, reversibility of observed toxic effects**

Non-clinical Lot(s) used in Toxicity Study

- **Ideally, same lot as used in clinical study and in compliance with GMP**
- **If this is not feasible, then preclinical should be comparable to the clinical material with respect to physico-chemical data, stability, formulation, etc**
  - **Lot release protocol**

Toxicity Assessment: Study Design

- **Dedicated stand alone toxicity studies *or***
- **Combination safety/activity study**
- **Control arms**
  - **Base line**
  - **Comparison to test group**
  - **Reversibility of adverse effects**
  - **Delayed adverse effects**

Toxicity Assessment: ROA/Dosing

- Route of administration (ROA) and dose should corresponded to clinically intended ROA and dose
- Total number of doses equal to or exceed number of clinically administered doses
  - [“N plus 1”]
- Episodic dosing, e.g., weeks between doses

Toxicity Assessment: Dose

- **Maximum human dose (1x)**
  - **In general, no need for dose response**
    - **Possible Exceptions (e.g., adjuvants)**
  - **Dose defined by the immune response**
  - **Volume**
    - **Same as administered to humans (1x)**
    - **Scale based on mg/kg, if 1x dose not feasible**
    - **Don’t change formulation**

Toxicity assessment: Parameters Monitored

- Local/systemic events
- Immunogenicity
- Clinical observations (general health, body weight and food consumption, injection site, limb use impairment)
- Serum chemistries including liver and renal function tests (ALT, AST, creatine kinase, BUN)
- Hematologic analysis (CBC and differential)
- Injection site histopathology
- Terminal procedures (necropsy, organ description, weights, histopathology on tissue including evaluation of immune organs)
- Good Laboratory Practice (GLP, 21 CFR 58.1)

Toxicity Assessment (cont.) Immune Response

- **Characterization of the immune response**
  - **Changes in immune parameters are expected**
  - **Parameters to be evaluated include white blood cell count, histopathological examination of bone marrow & lymphoid tissue**
- **Tiered testing approach**
  - **In some cases specific immune investigations may be necessary**
  - **Hypersensitivity reactions**

Toxicity Assessment: Animal Model

- "Relevant" animal species
  - An animal species susceptible to respond to the test article activity, e.g., development of an immune response after vaccination
    - Ideally, species should be sensitive to the pathogenic organism or toxin
  - One relevant animal species in general sufficient
    - Exceptions on a case-by-case
    - Non-human primates not generally necessary
  - Group size dependent on the animal model

Toxicity Assessment: Animal Model (cont.)

- **Additional considerations**
  - **Recognize limitations of animal model**
  - **Judicious use of animals**
  - **Use of naïve *vs*. partially immune or immune animals**
  - **Juvenile animal models???**
  - **Animal validation (e.g., historic control data such as hematological, serum chemistry parameters, pathology, etc.)**
- **Justify animal model!**

Special Considerations for Toxicity Assessments (cont.)

- **Adjuvants**
  - **Demonstrate effect in non-clinical immunogenicity study**
  - **Evaluate relevant vaccine/adjuvant formulations in preclinical GLP safety studies:**
    - **Vaccine product with and without adjuvant in preclinical studies**
    - **Antigen/adjuvant formulation intended for clinical use**
  - **If novel adjuvant, then safety assessment of adjuvant by itself**

Special Considerations for Toxicity Assessments

Developmental Toxicity Studies

- Considered if product includes females of child bearing potential or pregnant women
- Need for developmental toxicity study will depend on the product
- Restricted to pre- and postnatal developmental studies, no fertility and post-weaning assessment for most vaccine products
- Tiered approach
- CBER guidance revised to reflect this approach

Special Considerations for Toxicity Assessments (cont.)

- Genotoxicity studies: In general not needed
  - Exception adjuvant, excipient (case-by case)
- Carcinogenicty studies: In general not needed
- Safety pharmacology (circulatory/respiratory system): In general not needed, (case-by-case)
- Pharmacokinetic studies: In general not needed
  - Case-by case: novel adjuvants, alternate ROA

Timing of Preclinical Toxicity Studies

- Prior to initiating Phase 1 clinical trials
- Discuss with CBER prior to or during pre-IND meeting
  - Provide adequate information on clinical plan
- Submit toxicity protocols for CBER review prior to initiation of animal studies
  - Avoid additional toxicity studies
- Submit toxicity study report to original IND
  - Full tabulation of data, line listings
  - Safety of clinically intended dose/ROA
- Additional toxicity studies may be necessary as product/clinical development continues

CT Products: Special Considerations

- **Expeditious development and licensing of products to treat or prevent outbreaks from exposure to the pathogen identified as bioterrorist agents**
- **CBER guides products through the regulatory process**
  - **Manufacturing process, pre-clinical testing, clinical trials and approval process**

CT Products: Special Considerations

- Early and frequent communication with sponsor essential
- Need for pre-pre-IND CBER consult
  - Insure quality of toxicity studies
  - Reduce misunderstandings
  - Prevent unnecessary use of animals
  - Expedite initiation of Phase 1 clinical trials
  - Expedite product development

CT Products: Special Considerations

- **Significance of pre-clinical assessments:**
  - **CT product availability under IND**
    - **Potentially large numbers of healthy individuals**
  - **Acceptable basic safety data derived from *in vivo* or *in vitro* pre-clinical studies**
    - **Assure no unreasonable risk**
  - **“Proof-of-concept” studies provide reasonable scientific basis for activity**

CT Products: Special Considerations

- **Preclinical safety data help provide confidence that risk:benefit ratio favorable enough for timely product access**

Summary

- Non/pre-clinical safety assessment is a key component in vaccine development
  - Of special significance for CT products
- Case-by-case, science based
- Approach to optimal study and/or toxicity assessment for vaccines evolving
- Emphasis on early communications with sponsor
- Vaccine specific guidance for non-clinical safety assessment of vaccines currently being developed
  - WHO guideline on nonclinical evaluation of vaccines

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